Biomonitoring, *National Exposure Report*, Chemical Selection

John Osterloh, MD, MS
Chief Medical Officer
Division of Laboratory Sciences
National Center for Environmental Health

Public Health Mission

To prevent disease due to environmental chemicals, we must:

- Detect exposure or disease
- Assess health risks based on scientific evidence
- Implement interventions
- Assure those interventions are effective

Biomonitoring

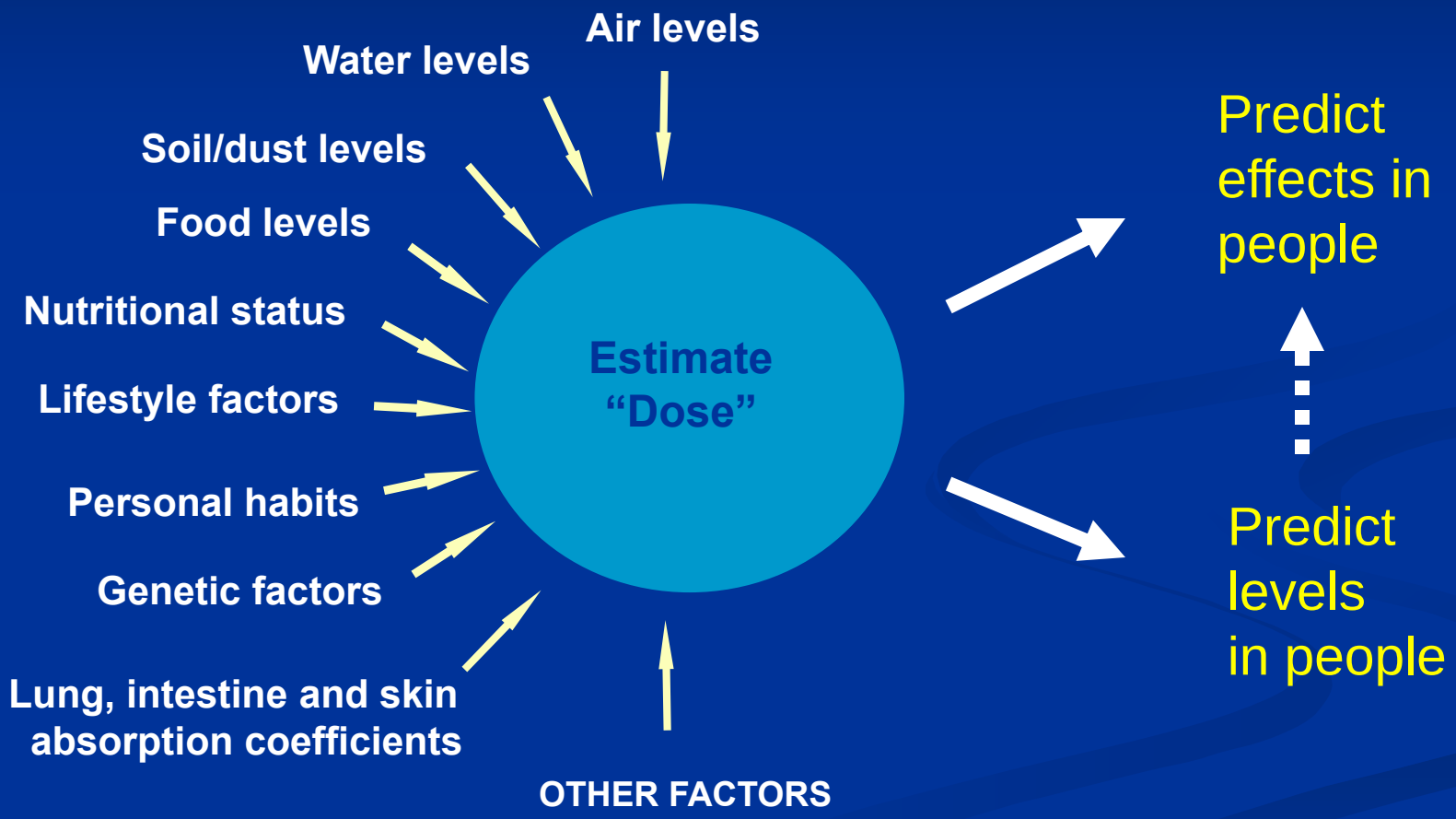
-the measurement of chemicals in blood and urine-

can help meet public health goals

Attributes of Biomonitoring

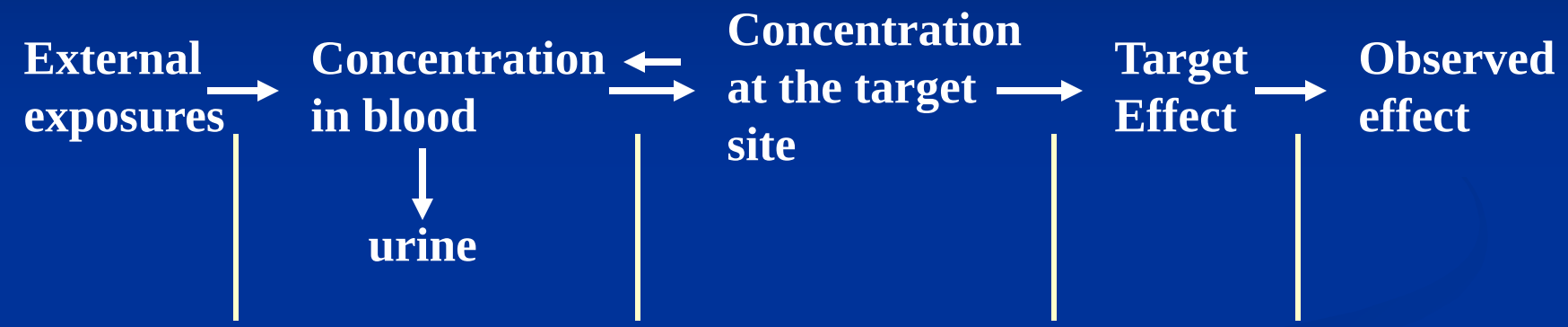
- A more direct indicator of exposure and internal dose (though not *the* dose) than traditional estimated intakes
  - Measurable, not estimated or averaged
  - Inclusive of multiple exposure routes
  - Fewer sources of variability between site of measurement and site of action
    - Potential metric for benchmarking effects

Traditional Dose Estimates



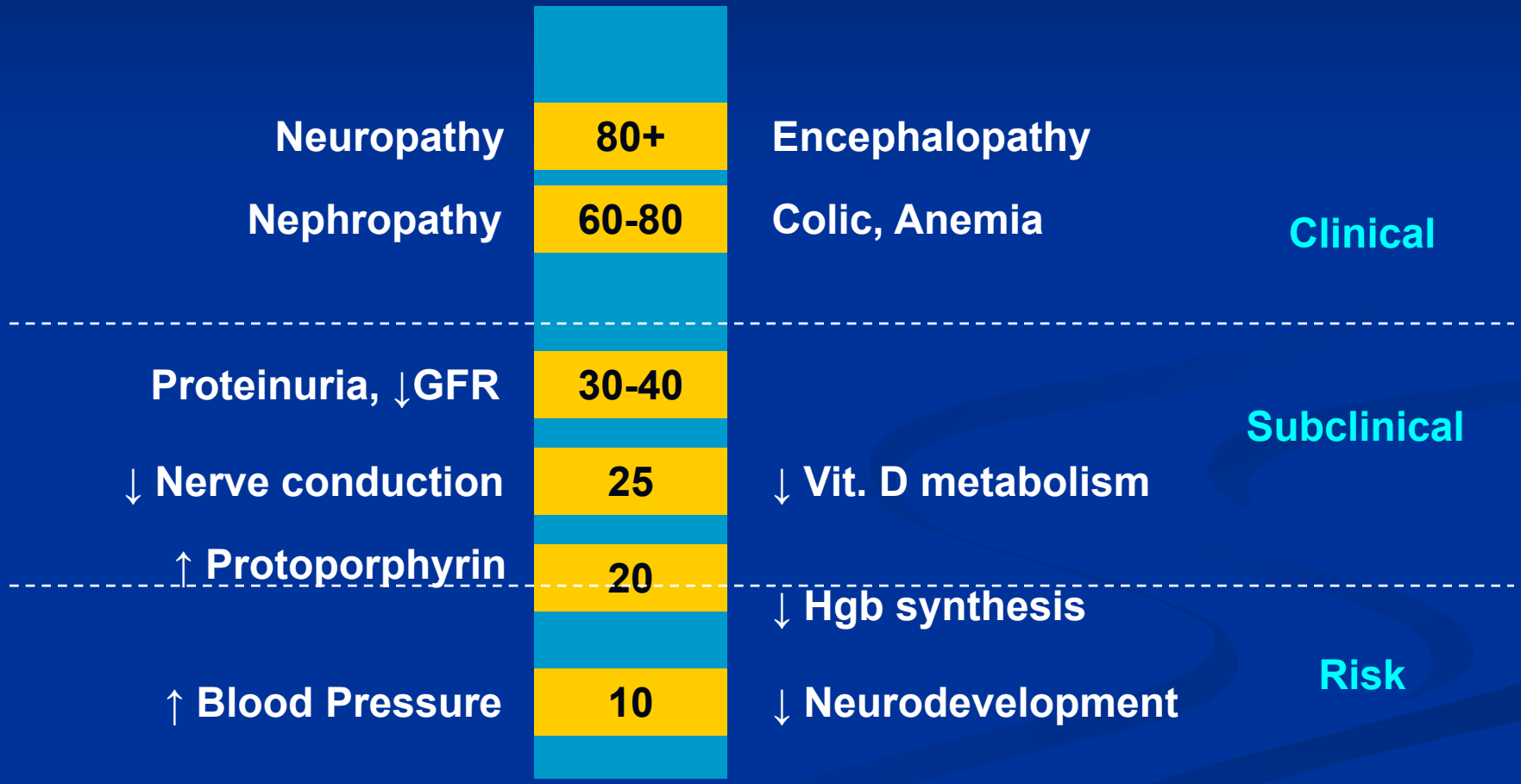
Exposure - Effect

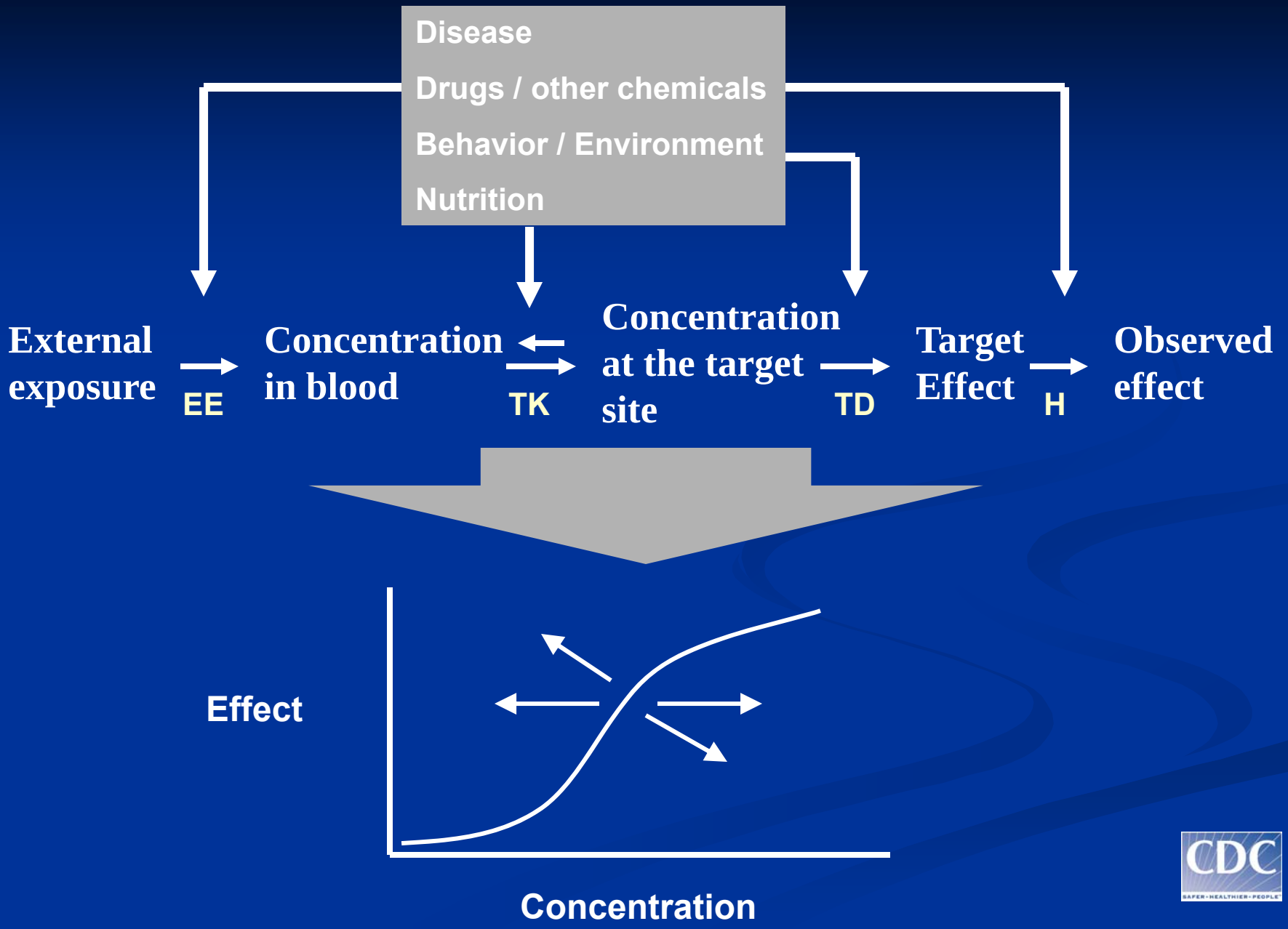
Sources of Variability



- **Exposure Estimate**
  - •Sources/Routes
  - •Amounts
  - •Duration
  - •Behaviors
  - •Absorption
- **Kinetics**
  - •Time
  - •Absorption
  - •Distribution
  - •Elimination
  - •Metabolism
- **Dynamics**
  - •Equilibrium
  - •Physiologic state
  - •Receptor status
  - •Cellular nutrition
- **Homeostasis**
  - •Physiologic antagonism
  - •Repair
  - •Metabolic compensation
  - •Receptor regulation

Blood Lead
-Effects Benchmarked to Levels-




Disease
Drugs / other chemicals
Behavior / Environment
Nutrition
External exposure
EE
Concentration in blood
TK
Concentration at the target site
TD
Target Effect
H
Observed effect
Effect
Concentration

Applications of Biomonitoring

- In Epidemiologic Investigations
  - Prevalence of excess exposure
  - Case definition
- For Research and Risk Estimation
  - Exposure assignment
  - Validation of external dose estimates
    - Dose-concentration relationships
  - Concentration-effect relationships
    - Benchmarking
  - Determinants of concentrations
- To Individuals for Health Care
  - For monitoring, screening, diagnosis. Requires:
    - Concentration-effect relationship
    - Clinical validation studies
- Population Surveys
  - Describing the public's exposure

CDC
SAFER·HEALTHIER·PEOPLE

Describing the Public's Exposure

- Who is exposed? How much?
- Which chemicals?
- Monitor time trends and interventions
- Prevalence above thresholds
- Assist in risk assessments
- Establish reference values
- Set new research directions

National Report on Human Exposure to Environmental Chemicals

National Center of Health Statistics

NHANES Mobile Examine Centers

Ongoing assessment of chemical exposure in U.S. population

National Exposure Report

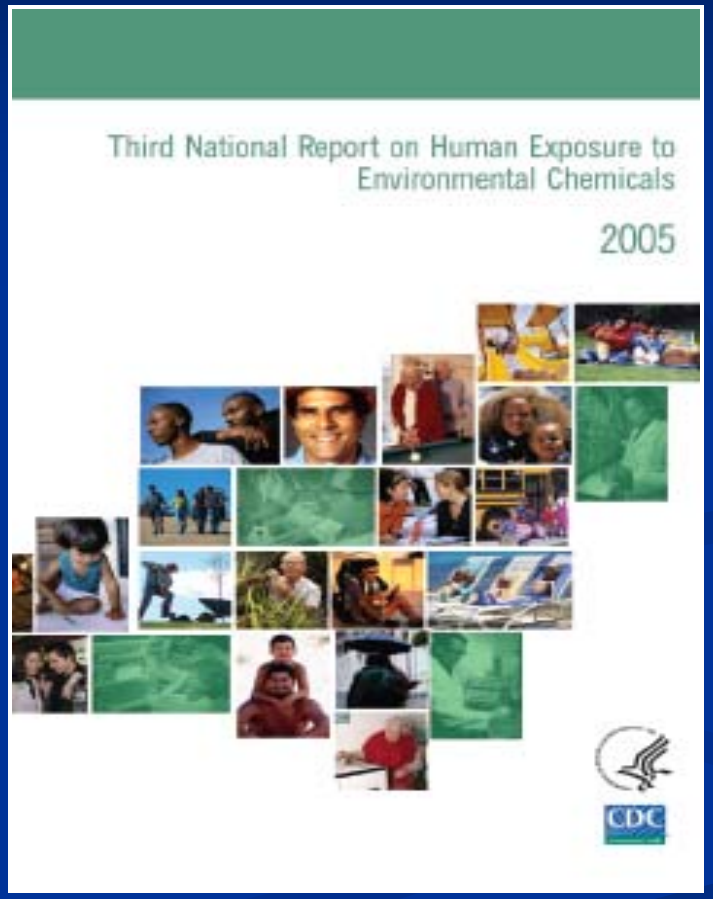
- National Health and Nutrition Examination Survey (NHANES)
  - Run by NCHS since 1971
  - Stratified, multistage, national probability sample
  - Since 1999, 8000 people every 2 years
  - 30 localities via mobile trailers
- Data collected
  - Extensive questionnaire on demographics and health behaviors
  - Physical exam
  - Medical and nutritional lab tests

National Exposure Report

- Blood or urine sampled from NHANES participants
  - A random 1/3rd subsample (most chemicals)
  - Sample size ~ 2500
  - In 3rd Report: over 350,000 high-quality analyses
- Descriptive
  - Geometric means, percentiles and confidence intervals
  - Age, gender, race/ethnicity
- Releases: 2001, 2003, 2005, 2008

148 Chemicals in *3rd Report*

- Metals
- Polychlorinated biphenyls, dioxins and furans
- Organochlorine pesticides
- Carbamate pesticides
- Organophosphate pesticides
- Herbicides
- Polycyclic aromatic hydrocarbons
- Phthalates
- Phytoestrogens
- Pest repellants
- Cotinine



www.cdc.gov/exposurereport

Most extensive evaluation of U.S. exposures

CDC
SAFER·HEALTHIER·PEOPLE

Fourth Release
Total ~ 265 Chemicals

New chemicals

- Speciated arsenic
- Polybrominated diphenyl ethers
- Fungicides
- Substituted Urea Herbicides
- Other new pesticides and metabolites
- Environmental Phenols
- Perfluorinated chemicals
- Volatile Organic Compounds
- Perchlorate
- Acrylamide

Limitations

- The presence of a chemical does not imply disease
  - More research needed
  - It's an exposure report
- Only aggregate levels (statistical point estimates) are representative of the U.S population.

  Individual levels are not representative, due to:
  - Collection timing
  - Inter-individual differences: kinetics, body size, other
  - Unique rather than ubiquitous exposure
- Data not representative of:
  - Locations, unexamined special groups, seasons, products
  - Sample not selected with regard to exposure or non-exposure

CDC
SAFER·HEALTHIER·PEOPLE

Impact of Biomonitoring Surveys

- Improved dose estimates and risk assessments:
  - Hg, perchlorate, dioxins, phthalates, PFOA
- Targeted research at human exposure levels
  - Phthalates, perchlorate
- Trends: Pb, cotinine, Hg, OCPs
- Comparisons of other populations to national values
  - Epi-investigations
  - Occupational exposures
  - Regional pesticide exposure studies
  - Other surveys: Germany, NYC

Developing Biomonitoring
Selection of Chemicals at DLS

- Chemicals of ongoing or emergent PH investigations for 30 years
  - e.g., dioxins, perchlorate
- Nomination "chemicals of interest"
  - One time process (so far)
  - Working group formed from NCEH Advisory panel (2002-3)
    - Developed criteria for nomination

Developing Biomonitoring
Nomination Criteria

- Potential for changing or persisting exposure to U.S. population
- Seriousness of suspected or known human health effects
- Proportion of population likely exposed
- A need to assess efficacy of public health actions
- Existence of an analytical method
- Incremental costs

Federal Register 2002;67(194): 62477

Developing Biomonitoring
Nomination Process

- *Fed Reg* March/02: Public comment on proposed criteria
- *Fed Reg* October/02: Final criteria and nominations solicited
- Nominations received: 400+ chemicals.
  - "Level of interest" scoring by toxicologist panel and division
  - Categorized into 5 levels of interest
- *Fed Reg* Sept/03: Posted nominations
  - No threshold for listing
  - No obligatory entry into Report *(interest!)*
- Nominations reflected existing plans at DLS
  - Did not influence chemicals first three *Reports*

Group 1 [in alphabetical order]

1,3-Butadiene
1-Decanesulfonic acid, 1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heneicosafluoro, ammonium salt
Aldicarb
Benzo[a]pyrene
Dichlorvos (DDVP)
Diesel exhaust
Dimethoate
Ethylene dibromide
Fonofos
Formaldehyde
Isodrin
Mancozeb
Manganese
Methyl bromide
N-methyl perfluorooctanesulfonamidoacetate (M570)
Octabromodiphenyl ether (OBDE)
Oxamyl
Pentabromodiphenyl ether (PeBDE)-congeners include BDE 82, 116, and 119
Perfluorinated carboxylic acid metabolites of telomer alcohol or telomer acrylate (n = 3)
Perfluorobutane sulfonate (PFBS)
Perfluorooctanoic acid fluoride
Perfluorooctanoic acid (PFOA) ammonium salt *
PFOA ethyl ester
PFOA free acid
PFOA methyl ester
PFOA potassium salt *
PFOA silver salt *
PFOA sodium salt*
Perfluorooctane sulfonate (PFOS) ammonium salt*
PFOS diethanolamine salt*
PFOS lithium salt*
PFOS potassium salt*
Phorate
Phosmet
trans Fatty acids

* PFOA and PFOS measured as a consequence of exposure to any PFOA or PFOS salt.

Developing Biomonitoring
Starting from Scratch

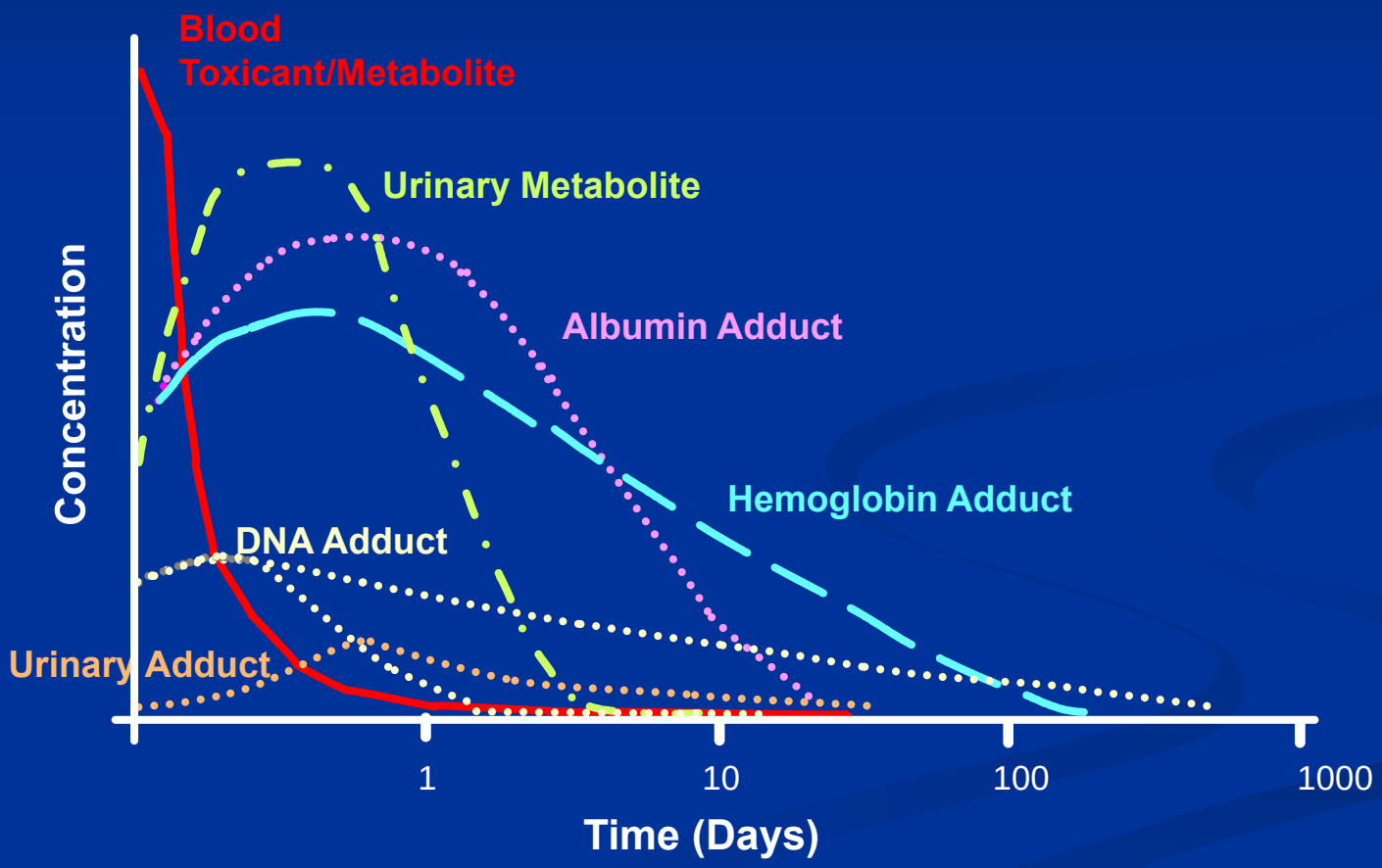
- Lists from other biomonitoring programs
  - Technology and public health
- Knowledge of regional chemicals
  - Production, use, and waste reports
  - Ongoing contamination events
  - Existing environmental measurements
    - Consider pairing with biomonitoring
- Survey the public, industry, advocacy groups
- Toxicity rankings

Developing Biomonitoring

- What is the best specimen?
  - Blood, urine, breath, saliva, nails, feces, hair, semen, fat, breast milk, meconium
    - Significant fraction of the dose or burden
    - Target organ exposure
  - Stable
  - Without interferences
  - Uncontaminated
- What is the best chemical form to measure?
  - Parent, metabolite, adduct?
  - Present, past, cumulative, integrated exposures?
  - Biomarkers of effect and biomarkers of exposure?

Concentration Time Course

Single Exposure: Non-persistent chemical



Modified from Needham and Sexton, JEAEE 10:611-629 (2000)

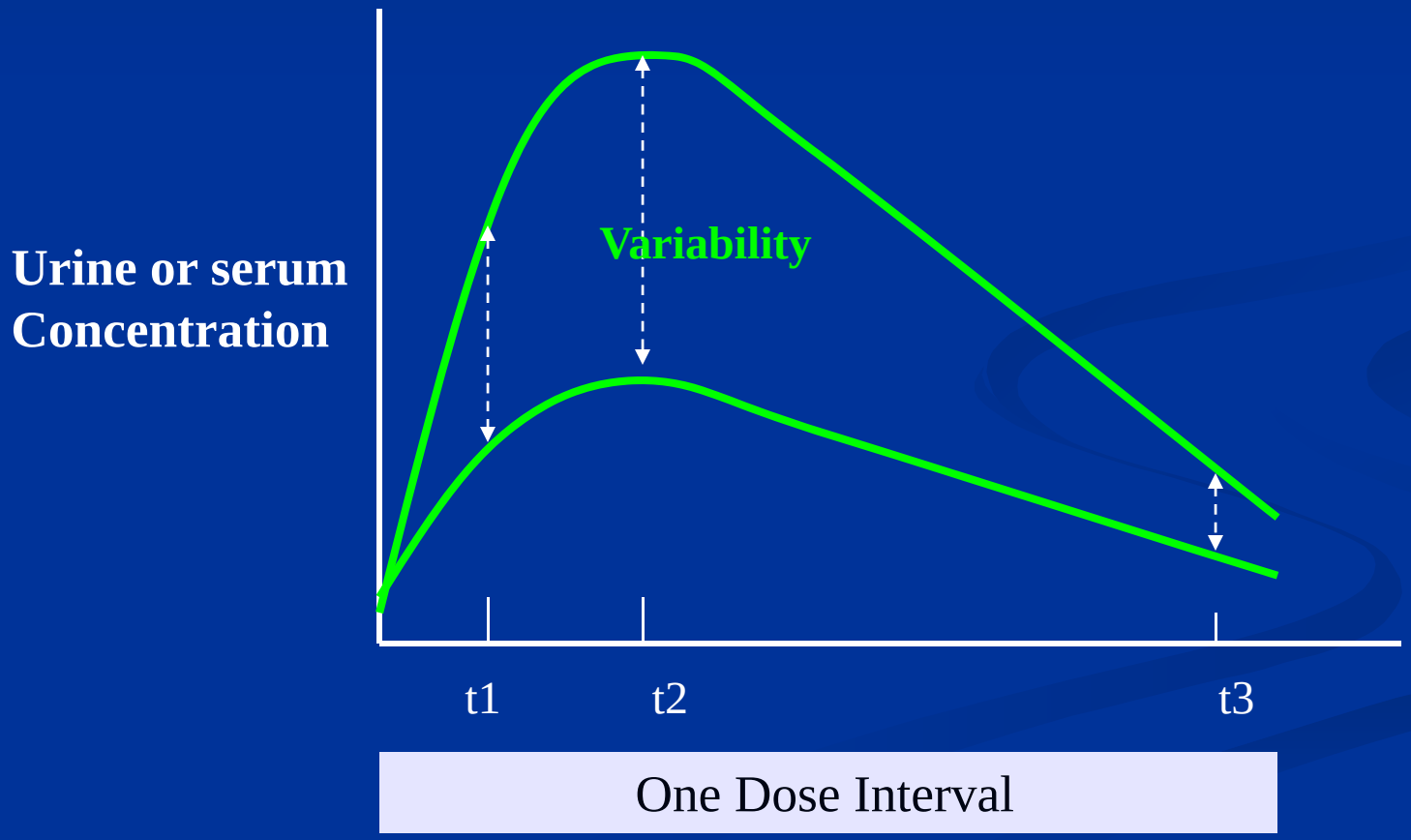
Developing Biomonitoring

- What is best time to collect specimens?
  - "Windows of opportunity"
    - Sample matrix, chemical form, half-life
    - Continuous or intermittent exposures
  - To represent effect or dose most precisely, consider toxicodynamic/toxicokinetic equilibria
    - Distributional (within dose)
    - Steady-state (over multiple doses)
    - Concentration-effect equilibrium
  - For large population samples-random effects
  - Individuals or small group comparisons-important
    - Standardize collection times

Distribution & Collection Time

e.g., non-persistent chemical

Time to measure: ***Time of least variability***

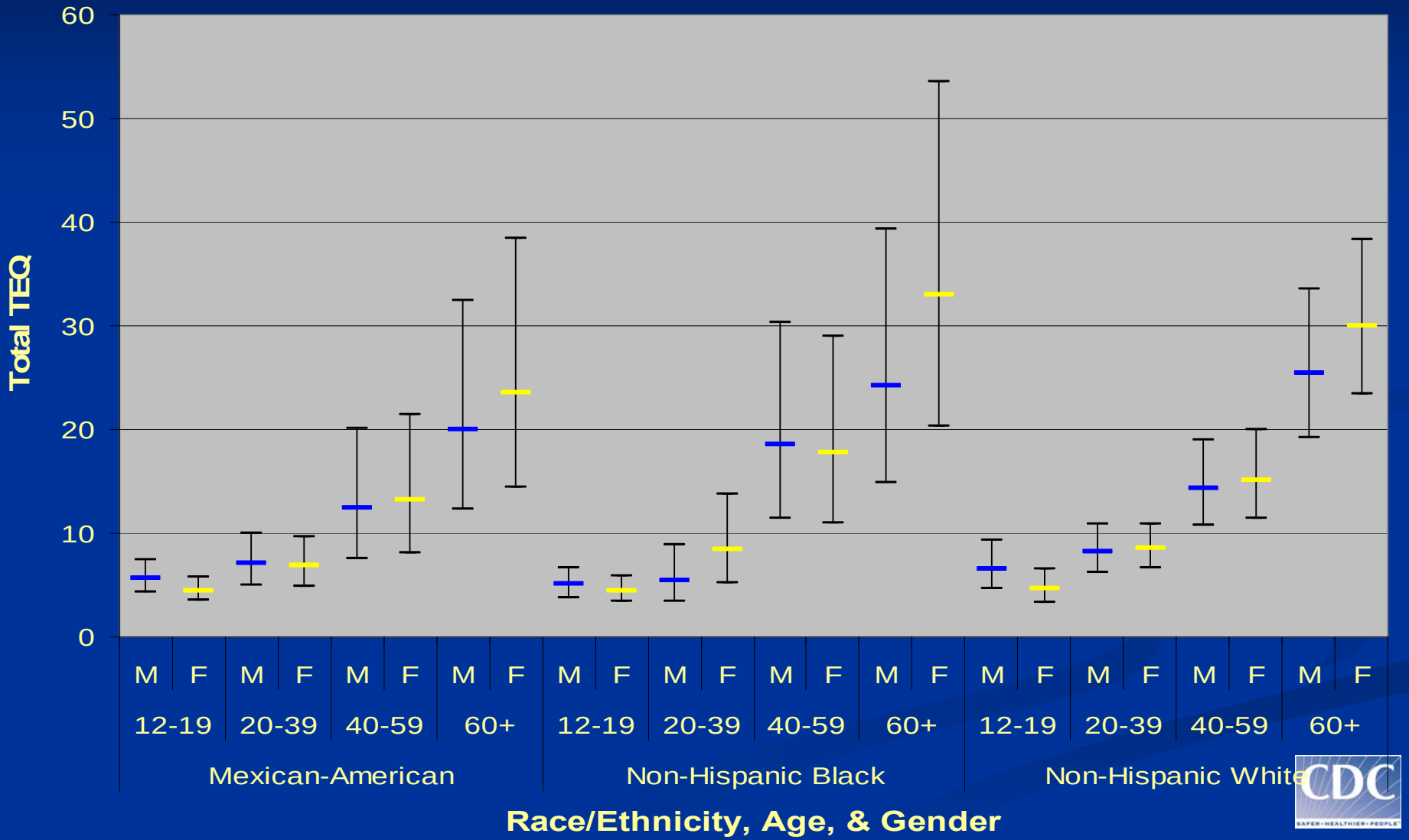


Developing Biomonitoring

- Type of survey sampling
  - Convenience (grab or volunteer):
    - cheap, easy, nonrepresentative
  - Targeted (stratified probability cluster):
    - requires census info
  - Random:
    - requires larger n, costly to assure
- Pooling from random or targeted surveys
  - Reduces analytic costs
  - Can improve LOD for some analytes

Dioxin-Like Chemical TEQs

NHANES Serum Pools, 2001-02



Developing Biomonitoring

Definitive reference methods are expensive

LC/MS/MS
ICP/MS
GC/MS/MS
GC/HRMS

Stable isotope internal standardization

Rigorous QA and contamination control

CDC
SAFER·HEALTHIER·PEOPLE

Developing Biomonitoring

- Selecting definitive techniques
- Optimizing conditions
- Define and validate
  - Calibration-response
  - LOD and selectivity
  - Accuracy and precision
- QC, PT, contamination control
- Throughput and ruggedness
- Safety and security

Interpretation of Biomonitoring Data

- Understanding the application?
  - Population point estimates vs. individual values
  - Inference (research) vs deduction (epi, med)
- Identification of unusual exposures
  - Well characterized LODs and background levels
- Health effects?
  - Concentration-effect relationships must be known
  - Comparable situations
- Understanding sources of imprecision and variability?
  - Analytic imprecision
  - Inter- and intra-subject
    - Timing, kinetics, demographics, behaviors, comorbidities
  - Relational imprecision

CDC
SAFER·HEALTHIER·PEOPLE

California and National Biomonitoring

- National data does not represent California (or any state)
- Comparisons: identify regions or populations with unusual exposure
  - Versus national or state data
  - e.g., NYC HANES
- Example: California and DDE

Table 1. *p,p'*-DDE (lipid adjusted)

Geometric mean and selected percentiles of serum concentrations (nanograms/gram [ng/g] of lipid or parts-per-billion on a lipid weight basis) for the U.S. population aged 12 years and older, National Health and Nutrition Examination Survey, 1999-2000.

	Geometric mean (95% conf. interval)	Selected percentiles (95% confidence interval)						Sample size
		10th	25th	50th	75th	90th	95th	
Total, age 12 and older	260 (234-289)	74.2 (66.1-84.2)	114 (99.8-129)	226 (191-267)	538 (485-609)	1120 (991-1290)	1780 (1520-2230)	1964
Age group								
12-19 years	118 (101-137)	45.9 (34.9-56.6)	69.8 (59.2-80.4)	108 (90.6-132)	185 (141-233)	343 (255-479)	528 (364-644)	686
20 years and older	297 (267-330)	86.0 (75.2-96.7)	130 (115-150)	269 (229-303)	626 (538-697)	1250 (1100-1420)	1990 (1570-2510)	1278
Gender								
Males	249 (221-281)	77.6 (68.6-88.2)	119 (101-133)	222 (182-266)	489 (383-570)	985 (756-1130)	1350 (1190-1610)	937
Females	270 (241-302)	68.9 (55.1-82.5)	112 (96.0-129)	228 (191-286)	604 (516-697)	1320 (1100-1600)	2150 (1650-2750)	1027
Race/ethnicity								
Mexican Americans	674 (572-795)	154 (133-214)	300 (252-370)	623 (505-750)	1350 (1090-1660)	3090 (2100-4610)	4940 (3280-7810)	657
Non-Hispanic blacks	295 (253-344)	62.2 (56.9-80.5)	113 (98.3-128)	203 (164-253)	452 (392-571)	1340 (974-1910)	2160 (1470-4010)	416
Non-Hispanic whites	217 (193-244)	73.0 (63.2-82.2)	107 (94.5-127)	197 (175-238)	459 (372-513)	852 (693-1010)	1220 (1040-1410)	732

DDE
Population Comparisons

- DDT banned in 1973
- DDE metabolite detected in 99.9%
- Measurable in 12-19 yr
  - Born after DDT ban
  - Persistence in environment: food
  - Breast milk transfer
- DDE is 3 times higher in Mexican-Americans
  - Sampling
  - Immigration
  - Work exposure
- California vs National?

Other Topics

- Oversight and scrutiny
  - Government, public, industry, and media inquiry
- Not known to be toxic, why measure?
- Biomonitoring not available for all chemicals
- Sample volume limitations
- Costs

Summary

- Complementary approach to estimate exposure or to benchmark with health effects
  - Reduces sources of variability
  - May relate better to target action
- Know applications and limitations
  - If no conc-effect, will not reveal health risks
  - Surveying populations, not individuals
    - Random effects and biases
- Biomonitoring surveys: prevalence, trends, reference values, improved risk assessment

Thank You